Visit-to-Visit Glycemic Variability and Risks of Cardiovascular Events and All-Cause Mortality: The ALLHAT Study

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OBJECTIVE

The prognostic value of long-term glycemic variability is incompletely understood. We evaluated the influence of visit-to-visit variability (VVV) of fasting blood glucose (FBG) on incident cardiovascular disease (CVD) and mortality.

RESEARCH DESIGN AND METHODS

We conducted a prospective cohort analysis including 4,982 participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) who attended the baseline, 24-month, and 48-month visits. VVV of FBG was defined as the SD or variability independent of the mean (VIM) across FBG measurements obtained at the three visits. Participants free of CVD during the first 48 months of the study were followed for incident CVD (coronary heart disease [CHD], stroke, and heart failure [HF]) and all-cause mortality.

RESULTS

Over a median follow-up of 5 years, there were 305 CVD events (189 CHD, 45 stroke, and 81 HF) and 154 deaths. The adjusted hazard ratio (HR) comparing participants in the highest versus lowest quartile of SD of FBG (≥26.4 vs. <5.5 mg/dL) was 1.43 (95% CI 0.93–2.19) for CVD and 2.22 (95% CI 1.22–4.04) for all-cause mortality. HR for VIM was 1.17 (95% CI 0.84–1.62) for CVD and 1.89 (95% CI 1.21–2.93) for all-cause mortality. Among individuals without diabetes, the highest quartile of SD of FBG (HR 2.67 [95% CI 0.14–6.25]) or VIM (HR 2.50 [95% CI 1.40–4.46]) conferred a higher risk of death.

CONCLUSIONS

Greater VVV of FBG is associated with increased mortality risk. Our data highlight the importance of achieving normal and consistent glycemic levels for improving clinical outcomes.

Diabetes is common in the U.S. (1). Glycemic impairment, including in the nondiabetic range, is an independent risk factor for cardiovascular disease (CVD) and overall mortality (2,3). Hitherto, studies investigating the hyperglycemia-related complications have mainly relied on punctual assessment of blood glucose, which may not capture the true underlying average levels over time. Glycemic variability has emerged as a measure that could more accurately capture the pathological processes presiding over the occurrence of complications. It is therefore a potentially important predictor of hyperglycemia-related complications, which would be highly relevant for prognosis.

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However, the extant evidence on the relation of glycemic variability and outcomes has remained limited, as it has mainly stemmed from studies that solely included people with diabetes and mostly focused on short-term variability of blood glucose levels (4–6). The prognostic significance of long-term visit-to-visit (VVV) glycemic variability largely remains understudied.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a multicenter trial of hypertension therapy, includes a large and diverse population of individuals (aged ≥55 years) with or without diabetes in whom fasting blood glucose (FBG) was assessed at multiple visits conducted at set time intervals. We therefore conducted an observational analysis of ALLHAT to assess the association of VVV in FBG with incident cardiovascular events and all-cause mortality among individuals with and without diabetes. We hypothesized that the incidence of cardiovascular events or mortality would be higher among individuals with a higher FBG variability.

RESEARCH DESIGN AND METHODS

Study Sample

We conducted a post hoc cohort analysis of data from ALLHAT, a multicenter randomized, double-blind clinical trial designed to determine whether treatment initiated with a calcium channel blocker (amlodipine), an ACE inhibitor (lisinopril), or an α-blocker (doxazosin), each compared with treatment initiated with a diuretic (chlorthalidone), would lower major cardiovascular outcomes. A description of the rationale and design of ALLHAT has previously been reported (7). The primary end point was incidence of fatal coronary heart disease (CHD) or nonfatal myocardial infarction. A total of 42,418 hypertensive adults aged 55 years or older with one or more additional risk factors for CVD were enrolled at 623 clinical sites across the U.S., Canada, Puerto Rico, and the U.S. Virgin Islands between February 1994 and January 1998. The doxazosin treatment arm was discontinued in 2000 owing to little chance of finding a benefit on CHD outcomes and an increased risk of CVD compared with the chlorthalidone arm (8,9).

For this study, we included participants with complete data on FBG at the baseline, 24-month, and 48-month visits. We did not extend the assessment of FBG beyond the 48-month visit to maximize the follow-up time. We excluded participants who had CVD events or died prior to the 48-month visit. We excluded participants from the doxazosin treatment arm of ALLHAT owing to the limited follow-up. The in-trial period lasted from 1994 to 2002. After trial completion, the posttrial follow-up of participants was continued through 2006. Participants were followed for an event from their 48-month visit until the occurrence of an outcome event or the end of follow-up. ALLHAT was approved by local institutional review boards, and all participants provided written informed consent. The current analysis was approved by the institutional review board of The Ohio State University.

Measures of Glycemic Variability

The exposure of interest was the intraindividual VVV of FBG. We focused on FBG ascertained at baseline, as well as at 24 months and 48 months following randomization. Using the average FBG at each of these three visits, we calculated VVV of FBG. The VVV of FBG was primarily defined as the intraindividual SD across visits. The alternative VVV of FBG metrics include *1*) the coefficient of variation (CV); *2*) the variability independent of the mean (VIM), which is calculated as $100 * SD/mean^{\beta}$, where β is the regression coefficient based on natural logarithm of SD on natural logarithm of mean; and *3*) the average successive variability (ASV), defined as the average absolute difference between successive values. All the aforementioned measures of variability have been previously described (10,11). Given that there are no internationally agreed upon gold standard measures of glycemic variability in general and of VVV in particular, we opted to include a wide range of measures, which would potentially capture different aspects of glycemic variability (12).

Outcomes

The outcomes were *1*) CVD events defined as a composite of major cardiovascular events (including fatal and nonfatal CHD, stroke, and heart failure [HF]) and *2*) all-cause mortality. The methods for ascertaining events in ALLHAT have previously been described (7,8,13). The study participants were followed from the end of the period during which the VVV of FBG was assessed (48-month visit) to the date of each outcome, their date of death, or end of ALLHAT follow-up.

Covariates

The covariates included demographic and clinical variables. These consisted of the baseline variables such as age, sex, race/ethnicity, education, region of residence, randomization assignment, current cigarette smoking, BMI, estimated glomerular filtration rate (eGFR) (estimated using the Chronic Kidney Disease Epidemiology Collaboration equation [14]), history of CVD (myocardial infarction/coronary arterial disease, revascularization, stroke, peripheral arterial disease, or HF), use of aspirin, and use of antihypertensive medication prior to ALLHAT randomization. In addition, data collected at visits conducted from baseline to 48 months (following randomization) were used to calculate the following covariates: mean FBG, mean systolic blood pressure (SBP), and mean total cholesterol. Diabetes status at the baseline visit was defined by *1*) a prior history of diabetes and/or use of diabetes medications or *2*) an FBG ≥126 mg/dL.

Statistical Analysis

The participants were categorized into quartiles of SD of FBG, and their characteristics (demographic and clinical) were assessed across these quartiles. The categorical variables were presented as proportions and continuous variables as mean (SD) or median (interquartile range). We used the Kruskal-Wallis or ANOVA test to compare continuous variables and the χ^2 test for comparing categorical variables.

We also used multivariable Cox proportional hazards regression models to calculate adjusted hazard ratios (HRs) for each outcome associated with glycemic variability. This was done modeling each measure of glycemic variability as a continuous variable and quartiles of each measure of FBG variability (SD, VIM, ASV, and CV) with the lowest quartile serving as the reference. Four nested models were constructed: model 1 included adjustment for age, race/ethnicity, sex, region of residence, and antihypertensive medication randomization assignment. Model 2 included additional adjustment for education, smoking status, BMI, average cholesterol levels, use of

aspirin, eGFR, history of CVD, and use of antihypertensive medications prior to ALLHAT randomization. Model 3 additionally included adjustment for average SBP over the assessment period. Model 4 additionally accounted for the average FBG over the assessment period, except for the VIM measure.

All analyses were performed with the use of SAS software, version 9.4 (SAS Institute). A P value of <0.05 (two sided) was considered to indicate statistical significance. Given the exploratory nature of the analyses, the results were reported at a nominal level.

RESULTS

Baseline Characteristics

Figure 1 shows the process of selection of participants in this study. Of the ALLHAT participants, 4,982 participants had an FBG assessment at the baseline, 24-month, and 48-month visits; did not experience a CVD event or die before 48 months; and had complete data on the covariates and were thus included in the following study. Of note, a significant proportion of ALLHAT participants were excluded because of missing FBG measures. Compared with those with adequate FBG data, the participants without FBG at follow-up were more likely to be black or female, be a current smoker, or have diabetes or elevated blood pressure (Supplementary Table 1).

The characteristics of the participants included in this study across quartiles of SD of FBG are presented in Table 1. The participants in the highest quartile of FBG SD were younger, more likely to be black or to have diabetes, and less likely to be taking aspirin prior to baseline. They also had a higher BMI, eGFR, and mean SBP. Participants randomized to chlorthalidone were more likely, while those randomized to lisinopril were less likely, to be in the highest quartiles of SD of FBG.

Over a median follow-up period of 5 years (range 4–8), there were 305 CVD events (189 cases of CHD, 45 cases of stroke, and 81 cases of HF) and 154 deaths. The causes of deaths were categorized as follows: cancer (n = 36); other non-CVD causes (n = 36); CHD (n = 35); other CVD (n = 12); stroke (n = 10); congestive HF (n = 7); accidents, suicide, and homicide (n = 7); kidney disease (n = 1); and unknown (n = 10).

Measures of Glycemic Variability and Outcomes in the Overall Sample

As shown in Table 2, when glycemic variability was examined continuously in the fully adjusted model (model 4 [model 3 for VIM]), each unit change in VIM was associated with a higher risk of death (HR 1.014 [95% CI 1.006–1.022]; P = 0.001) but not of CVD events (HR 1.005 [95% CI 0.997–1.014]; P = 0.232). The association of each unit change in SD of FBG, ASV, or CV and the risks of death or cardiovascular events was borderline significant (Table 2).

After full multivariable adjustment (model 4 [model 3 for VIM]) (Tables 3 and 4), when compared with the lowest quartile, participants in the highest quartile of SD of FBG had a significantly higher risk for death (HR 2.22 [95% CI 1.22–4.04]) but not for CVD (HR 1.43 [95% CI 0.93–2.19]). Similar results were observed with other measures of VVV of FBG including CV and VIM (Tables 3 and 4). When compared with the lowest quartile (Tables 3 and 4), the highest quartile of CV conferred a higher risk of death (HR 2.00 [95% CI 1.18–3.41]) but not of CVD (HR 1.26 [95% CI 0.86–1.85]). In comparison with the lowest quartile of VIM, the highest quartile was associated with a higher risk of death (HR 1.89 [95% CI 1.21–2.93]) but not of CVD (HR 1.17 [95% CI 0.84–1.62]). The highest quartile of ASV (vs. the lowest quartile) was not associated with a higher risk of death (HR 1.79 [95% CI 0.98–3.28]) or CVD (HR 1.22 [95% CI 0.80–1.85]).

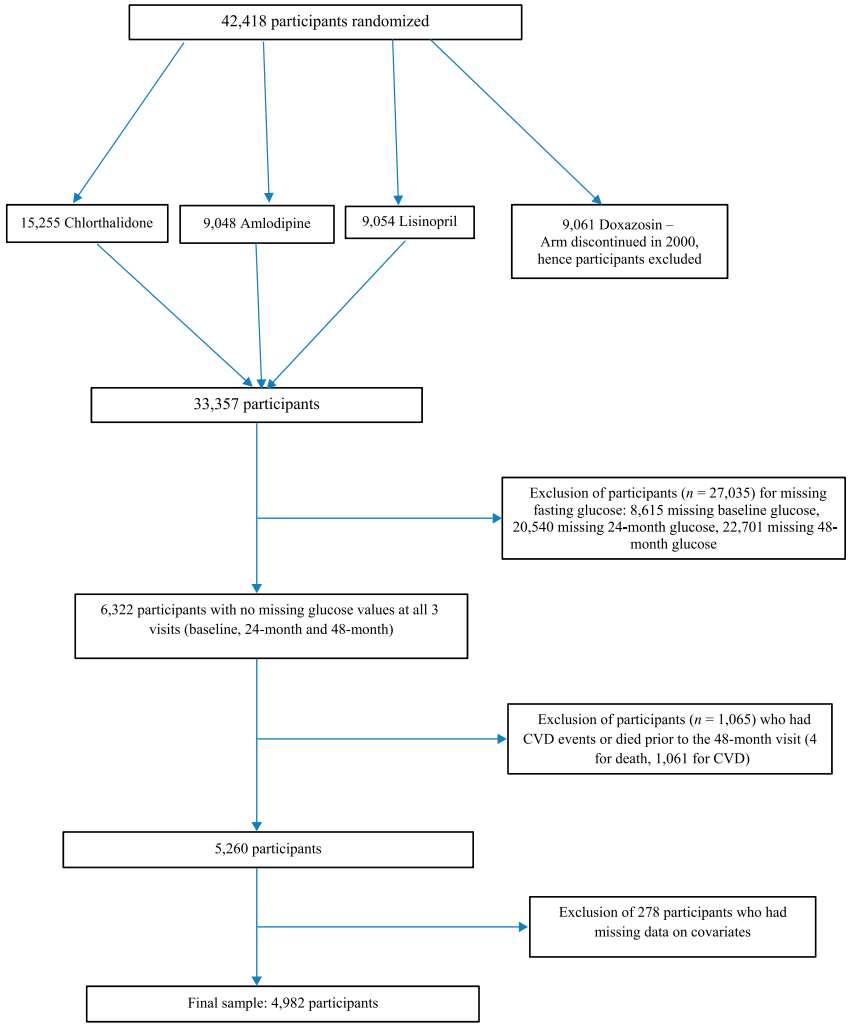

Figure 1—Study participants' selection process.

Table 1—Baseline characteristics of patients by quartiles of SD of fasting plasma glucose

	Total	Q1 (0–5.5 mg/dL)	Q2 (5.5–10.5 mg/dL)	Q3 (10.5–26.4 mg/dL)	Q4 (26.4–240.2 mg/dL)	*P*
n	4,982	1,217	1,276	1,244	1,245	
Age, years	65 (60–70)	66 (61–71)	66 (61–71)	65 (60–71)	64 (60, 69)	<0.0001
Male sex	2,840 (57.0)	665 (54.6)	754 (59.1)	748 (60.1)	673 (54.1)	0.002
Race						<0.0001
White and other	3,564 (71.5)	926 (76.1)	957 (75.0)	884 (71.1)	797 (64.0)	
Black	1,418 (28.5)	291 (23.9)	319 (25.0)	360 (28.9)	448 (36.0)	
Ethnicity						0.511
Non-Hispanic	3,622 (72.7)	890 (73.1)	946 (74.1)	908 (73.0)	878 (70.5)	
Hispanic	1,035 (20.8)	244 (20.1)	254 (19.9)	254 (20.4)	283 (22.7)	
Other	325 (6.5)	83 (6.8)	76 (6.0)	82 (6.6)	84 (6.8)	
Education (number of years)	12 (9, 14)	12 (9, 14)	12 (9, 14)	12 (9, 14)	12 (9, 13)	0.0002
Smoking status						<0.0001
Current	1,012 (20.3)	243 (20.0)	311 (24.4)	271 (21.8)	187 (15.0)	
Past	2,093 (42.0)	503 (41.3)	535 (41.9)	522 (42.0)	533 (42.8)	
Never	1,877 (37.7)	471 (38.7)	430 (33.7)	451 (36.2)	525 (42.2)	
Region of residence						<0.0001
East	747 (15.0)	164 (13.5)	192 (15.1)	204 (16.4)	187 (15.0)	
Midwest	1,087 (21.8)	316 (26.0)	300 (23.5)	259 (20.8)	212 (17.0)	
South	1,464 (29.4)	302 (24.8)	364 (28.5)	373 (30.0)	425 (34.1)	
West	647 (13.0)	178 (14.6)	166 (13.0)	158 (12.7)	145 (11.7)	
Canada	127 (2.6)	31 (2.6)	38 (3.0)	32 (2.6)	26 (2.1)	
Puerto Rico and Virgin Islands	910 (18.3)	226 (18.6)	216 (16.9)	218 (17.5)	250 (20.1)	
Randomization group						0.002
Chlorthalidone	2,363 (47.4)	527 (43.3)	600 (47.0)	599 (48.1)	637 (51.2)	
Amlodipine	1,377 (27.6)	347 (28.5)	342 (26.8)	358 (28.8)	330 (26.5)	
Lisinopril	1,242 (24.9)	343 (28.2)	334 (26.2)	287 (23.1)	278 (22.3)	
Diabetes	1,758 (35.3)	64 (5.3)	156 (12.2)	502 (40.4)	1,036 (83.2)	<0.0001
History of CVD	1,276 (25.6)	338 (27.8)	380 (29.8)	318 (25.6)	240 (19.3)	<0.0001
Use of aspirin	1,816 (36.5)	472 (38.8)	498 (39.0)	456 (36.7)	390 (31.3)	0.0001
Use of hypertension medications	4,535 (91.0)	1,099 (90.3)	1,159 (90.8)	1,132 (91.0)	1,145 (92.0)	0.534
Baseline FBG, mg/dL	99 (89–126)	93 (87–99)	94 (86–104)	104 (90–130)	153 (113–205)	<0.0001
24-month FBG, mg/dL	103 (91–134)	93 (88–100)	96 (89–107)	113 (96–136)	162 (122–205)	<0.0001
48-month FBG, mg/dL	105 (93–134)	94 (89–101)	100 (91–108)	117 (102–139)	158 (120–205)	<0.0001
Cholesterol, mg/dL	205.1 (34.3)	205.3 (32.2)	205.3 (32.6)	203.7 (34.6)	206.2 (37.5)	0.298
Baseline BMI, kg/m^2	29.6 (5.6)	28.7 (5.4)	28.8 (5.3)	30.1 (5.7)	30.9 (5.5)	<0.0001
Baseline eGFR, mL/min/1.73 m^2	79.4 (18.5)	77.0 (16.5)	76.6 (16.8)	79.1 (18.4)	85.0 (20.6)	<0.0001
SBP, mmHg	136.9 (9.8)	136.0 (10.0)	136.4 (9.7)	137.3 (9.6)	137.7 (9.7)	<0.0001

Data are mean (SD) or median (quartile 1–quartile 3) for continuous variables and *n* (%) for categorical variables. Q, quartile.

Measures of Glycemic Variability and Outcomes by Diabetes Status

Glycemic Variability and Outcomes Among Participants With Diabetes

Among those with diabetes (Supplementary Table 2), each unit change in SD of FBG was not associated with incident death (HR 1.001 [95% CI 0.992–1.011]) or incident CVD events (HR 1.001 [95% CI 0.995–1.008]) in the fully adjusted model (model 4 [model 3 for VIM]). Each unit change in ASV, CV, or VIM was also not associated with incident death or CVD (Supplementary Table 2).

In participants with diabetes (Supplementary Table 3), when compared with the lowest quartile, the highest quartile of the SD of FBG was associated with neither incident death (HR 0.76 [95% CI 0.26–2.23]) nor CVD (HR 1.83 [95% CI 0.44–7.61]) in the fully adjusted model (model 4 [model 3 for VIM]). A similar pattern was observed with other measures of VVV of FBG including ASV, CV, and VIM (Supplementary Table 4).

Glycemic Variability and Outcomes Among Participants Without Diabetes

Among those without diabetes (Supplementary Table 2), each unit change in SD of FBG was significantly associated with incident death (HR 1.013 [95% CI 1.004–1.023]; $P < 0.05$) but not with incident CVD events (HR 1.006 [95% CI 0.997–1.015]) in the fully adjusted model (model 4 [model 3 for VIM]). Similar patterns were also observed for each unit change in ASV but not for each unit change in VIM (Supplementary Table 2), which was associated with both incident death (HR 1.023 [95% CI 1.013–1.034]; $P < 0.05$) and CVD (HR 1.012 [95% CI 1.002–1.023]).

Among participants without diabetes, compared with the lowest quartile (Supplementary Table 4), the highest quartile of SD of FBG conferred a higher risk of death (HR 2.67 [95% CI 1.14–6.25]) but not of CVD (HR 1.65 [95% CI 0.90–3.02]) in the fully adjusted model (model 4 [model 3 for VIM]). Similar results were observed with VIM (HR for mortality 2.50 [95% CI 1.40–4.46] and

Table 2—VVV in FBG as a continuous variable and incident events

	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
All-cause mortality								
SD	1.006 (1.001–1.011)	0.010	1.007 (1.002–1.012)	0.005	1.007 (1.002–1.012)	0.005	1.005 (0.998–1.012)	0.181
ASV	1.004 (1.00–1.008)	0.035	1.004 (1.001–1.008)	0.019	1.004 (1.001–1.008)	0.020	1.002 (0.997–1.007)	0.439
CV	1.015 (1.005–1.025)	0.003	1.016 (1.006–1.026)	0.002	1.016 (1.006–1.026)	0.002	1.013 (1.001–1.026)	0.036
VIM	1.015 (1.007–1.024)	0.0004	1.014 (1.006–1.022)	0.001	1.014 (1.006–1.022)	0.001	NA	NA
Cardiovascular events								
SD	1.006 (1.002–1.01)	0.002	1.006 (1.003–1.01)	0.0007	1.006 (1.002–1.01)	0.001	1.003 (0.997–1.008)	0.375
ASV	1.004 (1.001–1.007)	0.003	1.004 (1.002–1.007)	0.002	1.004 (1.001–1.007)	0.003	1.001 (0.997–1.005)	0.525
CV	1.01 (1.003–1.018)	0.006	1.011 (1.003–1.019)	0.005	1.011 (1.003–1.019)	0.007	1.005 (0.996–1.014)	0.312
VIM	1.006 (0.997–1.014)	0.181	1.005 (0.997–1.014)	0.210	1.005 (0.997–1.014)	0.232	NA	NA

Model 1: includes adjustment for age, race/ethnicity, sex, region of residence, and antihypertensive medication randomization assignment. Model 2: additional adjustment for education, smoking status, BMI, use of aspirin, average cholesterol, eGFR, history of CVD, and use of antihypertensive medications. Model 3: additional adjustment for average SBP. Model 4: additional adjustment for average FBG. NA, not applicable.

HR for CVD 1.30 [95% CI 0.84–2.02]) and other measures of VVV of FBG, except for ASV, which was associated with neither death nor CVD (Supplementary Table 4).

In sensitivity analyses restricted to individuals without diabetes at the 48-month visit, similar results between the indices of glycemic variability and the outcomes (mortality and cardiovascular events) were observed among individuals free of diabetes over the entire observation period (Supplementary Tables 5–7).

Table 3—VVV in FBG as a categorical variable and incident mortality

Measures of variability	Estimate of association, HR (95% CI)			
	Model 1	Model 2	Model 3	Model 4
Quartiles of SD				
Q1 (0–5.5)	Reference	Reference	Reference	Reference
Q2 (5.5–10.5)	1.16 (0.70–1.93)	1.13 (0.68–1.88)	1.13 (0.68–1.88)	1.13 (0.68–1.88)
Q3 (10.5–26.4)	1.81 (1.12–2.91)	1.83 (1.13–2.95)	1.83 (1.13–2.95)	1.82 (1.11–2.98)
Q4 (26.4–240.2)	2.03 (1.26–3.28)	2.23 (1.36–3.63)	2.23 (1.36–3.63)	2.22 (1.22–4.04)
Quartiles of ASV				
Q1 (0–6.0)	Reference	Reference	Reference	Reference
Q2 (6.5–12.5)	1.10 (0.66–1.84)	1.10 (0.66–1.86)	1.11 (0.66–1.86)	1.10 (0.65–1.84)
Q3 (13.0–31.5)	2.01 (1.26–3.20)	2.00 (1.25–3.20)	2.00 (1.25–3.20)	1.94 (1.20–3.13)
Q4 (32.0–405.0)	1.82 (1.12–2.97)	2.00 (1.21–3.29)	2.00 (1.21–3.29)	1.79 (0.98–3.28)
Quartiles of CV				
Q1 (0–5.6)	Reference	Reference	Reference	Reference
Q2 (5.6–9.9)	0.94 (0.56–1.60)	0.93 (0.55–1.58)	0.93 (0.55–1.58)	0.93 (0.55–1.57)
Q3 (9.9–19.7)	1.82 (1.15–2.89)	1.83 (1.15–2.92)	1.83 (1.15–2.91)	1.80 (1.12–2.88)
Q4 (19.7–94.6)	1.97 (1.24–3.14)	2.12 (1.32–3.41)	2.12 (1.32–3.40)	2.00 (1.18–3.41)
Quartiles of VIM				
Q1 (0–7.4)	Reference	Reference	Reference	Reference
Q2 (7.4–12.2)	0.96 (0.58–1.58)	0.98 (0.60–1.62)	0.98 (0.60–1.62)	NA
Q3 (12.2–19.3)	1.05 (0.65–1.69)	1.03 (0.64–1.67)	1.03 (0.64–1.66)	NA
Q4 (19.3–258.7)	1.87 (1.21–2.91)	1.89 (1.22–2.94)	1.89 (1.22–2.93)	NA

Unit of each quartile of the measure of variability is mg/dL. Model 1: includes adjustment for age, race/ethnicity, sex, region of residence, and antihypertensive medication randomization assignment. Model 2: additional adjustment for education, smoking status, BMI, use of aspirin, average cholesterol, eGFR, history of CVD, and use of antihypertensive medications. Model 3: additional adjustment for average SBP. Model 4: additional adjustment for average FBG. NA, not applicable; Q, quartile.

CONCLUSIONS

In a large sample of participants without diabetes and participants with diabetes in ALLHAT, we examined the influence of glycemic variability on outcomes. In this secondary analysis of ALLHAT, we observed a positive association between FBG variability and overall mortality but not incident cardiovascular events. The positive association of glycemic variability and mortality was significant and greater in magnitude among people without diabetes compared with those with diabetes. The direction and the magnitude of these associations were roughly consistent across measures of variability, and these remained significant for several measures of variability even after adjustment for the mean glucose, suggesting an intrinsic effect of FBG variability. The differences between glycemic variability measures in terms of magnitude and significance of the observed associations with outcomes suggest that these measures probably capture different aspects of variability (12). Our results suggest that VIM is possibly a robust measure of VVV in glycemia, though from a clinical standpoint it may be premature to recommend one measure against another. Our findings add to the growing body of evidence on the prognostic value of glycemic variability and highlight the importance of more uniform and less variable glycemia.

Our study expands on the findings from previous studies that have also shown an association of glycemic variability with mortality (4,15) and CVD (4,5,15). However, these previous studies have been limited by their small size, the restriction to individuals with diabetes only, the noninclusion of racially/ethnically diverse samples, a variable interval between visits at which glycemia was assessed (ranging from days to months), and the methodologies used to estimate variability (4,5). All these

Table 4—VVV in FBG as a categorical variable and incident cardiovascular events

Measures of variability	Estimate of association, HR (95% CI)			
	Model 1	Model 2	Model 3	Model 4
Quartiles of SD				
Q1 (0–5.5)	Reference	Reference	Reference	Reference
Q2 (5.5–10.5)	1.26 (0.90–1.77)	1.23 (0.87–1.72)	1.22 (0.87–1.72)	1.20 (0.86–1.69)
Q3 (10.5–26.4)	1.33 (0.95–1.87)	1.32 (0.94–1.85)	1.31 (0.93–1.84)	1.21 (0.85–1.72)
Q4 (26.4–240.2)	1.73 (1.24–2.41)	1.80 (1.28–2.54)	1.78 (1.27–2.51)	1.43 (0.93–2.19)
Quartiles of ASV				
Q1 (0–6.0)	Reference	Reference	Reference	Reference
Q2 (6.5–12.5)	1.01 (0.72–1.42)	0.99 (0.70–1.39)	0.99 (0.70–1.39)	0.97 (0.69–1.36)
Q3 (13.0–31.5)	1.39 (1.01–1.93)	1.38 (1.00–1.92)	1.36 (0.98–1.89)	1.26 (0.90–1.76)
Q4 (32.0–405.0)	1.50 (1.08–2.09)	1.58 (1.13–2.22)	1.56 (1.11–2.19)	1.22 (0.80–1.85)
Quartiles of CV				
Q1 (0–5.6)	Reference	Reference	Reference	Reference
Q2 (5.6–9.9)	1.17 (0.84–1.63)	1.15 (0.83–1.60)	1.15 (0.82–1.60)	1.12 (0.80–1.55)
Q3 (9.9–19.7)	1.21 (0.87–1.69)	1.20 (0.86–1.67)	1.19 (0.85–1.66)	1.09 (0.78–1.54)
Q4 (19.7–94.6)	1.55 (1.12–2.14)	1.59 (1.14–2.21)	1.57 (1.13–2.19)	1.26 (0.86–1.85)
Quartiles of VIM				
Q1 (0–7.4)	Reference	Reference	Reference	Reference
Q2 (7.4–12.2)	1.02 (0.73–1.41)	1.00 (0.72–1.38)	0.99 (0.72–1.38)	NA
Q3 (12.2–19.3)	1.15 (0.84–1.58)	1.14 (0.83–1.57)	1.14 (0.83–1.56)	NA
Q4 (19.3–258.7)	1.18 (0.85–1.63)	1.17 (0.84–1.62)	1.16 (0.84–1.60)	NA

Unit of each quartile of the measure of variability is mg/dL. Model 1: includes adjustment for age, race/ethnicity, sex, region of residence, and antihypertensive randomization assignment. Model 2: additional adjustment for education, smoking status, BMI, use of aspirin, average cholesterol, eGFR, history of CVD, and use of antihypertensive medications. Model 3: additional adjustment for average SBP. Model 4: additional adjustment for average FBG. NA, not applicable.

factors not only would influence variability of FBG but also could impact the strength of the association with outcomes. We studied long-term glycemic variability, as prior studies have suggested that unlike short-term glycemic variability, long-term glycemic variability may predict complications in both type 1 and type 2 diabetes (4). While prior studies have focused on people with diabetes (4,5), there is robust evidence to suggest that the pathophysiological changes associated with glycemic fluctuations compared with stable glucose levels, including higher levels of inflammatory cytokines and the resulting endothelial dysfunction, are manifest in both individuals with normoglycemia and individuals with diabetes (16,17). Thus, in contrast with previous studies, we examined the influence of glycemic variability among those with diabetes and those without diabetes. The exploration of the latter group was based on prior mechanistic studies suggesting the possible deleterious effect of glycemic variability among individuals without diabetes (17–19)—a suggestion confirmed by our findings. Furthermore, a positive association between VVV of HbA_{1c} and all-cause mortality has been described among individuals without diabetes in a prior study (20).

The lack of association of glycemic variability with outcomes among those with diabetes may be due to a number of factors, including the use of diabetes medications in this subgroup that may have blunted glycemic variability, as well as the possible underestimation of the number of diabetes cases, as we did not have data on HbA_{1c} or 2-h postload glucose, especially as 2-h postload glucose variability may be strongly associated with outcomes (21). It is also possible that long-term glycemic variability matters more among those without diabetes, and among those with diabetes short-term variability is a predictor of outcomes.

The lack of association of FBG variability with CVD events is apparently at variance with results of previous studies (4–6). This apparent difference may in fact not be one, as some previous studies included clinical trial data with an intensive glucose-lowering arm and a standard glucose-lowering arm. A significant association between glycemic variability and outcomes (CVD or mortality) was only observed in the intensive glucose-lowering arm (22,23). In the standard glucose-lowering arm, there was no significant association between glycemic variability and outcomes. The latter is consistent with our results, as in ALLHAT there was a standard approach to blood glucose lowering. The fact that positive findings from these clinical trials were only observed in the intensive treatment arm suggests that hypoglycemia may have played a role.

Several aspects of our study differ from prior investigations, including differences in the population structure (in terms of age, ethnicity, and spectrum of glycemia captured [from normoglycemia to diabetes]); the use of glycemic markers other than FBG, e.g., HbA_{1c}; and, possibly, a lower variability in our cohort, given that most previous reports only included people with diabetes, who are more likely to have a higher glycemic variability. The differential association of glycemic variability with mortality and CVD could be related to a differential influence of glycemic variability on the occurrence of various complications, with possibly small glycemic variability significantly associated with microvascular complications compared with macrovascular complications (4–6). Microvascular complications could have contributed to mortality in addition to macrovascular disease. Although the available causes of death do not seem to show that this was the case, it is important to note that microvascular complications of diabetes are generally not recorded as primary causes of death. Conditions other than diabetes vascular complications, such as cancer, may have also contributed to higher mortality.

The exact mechanisms linking increased glycemic variability to an increased risk of adverse outcomes are unknown, but there are several hypotheses. Glycemic fluctuations may generate endothelial dysfunction and ultimately atherosclerosis, triggered by higher circulating levels of inflammatory cytokines and monocyte/macrophage adhesion to endothelial cells, as well as oxidative stress induced by glucose oscillations (16,17,24,25). Insulin, due to its antioxidant action, could affect the generation of oxidative stress and thus the effect of glucose variability (26). An inadequate cell antioxidant defense mechanism to oscillating glucose can favor diabetes complications (27–29).

Genes involved in free radical detoxification were shown to be downregulated during phases of acute hyperglycemia in normal individuals (30). Glucose variability could also influence the appearance of a "metabolic memory" in vascular cells (31). Transient hyperglycemia can cause long-lasting epigenetic changes (32), which promote systemic inflammation. Glycemic oscillations have also been shown to cause apoptosis of pancreatic β-cells (33), which may result in deterioration of glycemic control (34) and subsequent progression of complications.

The strengths of our study include a large and multiethnic sample of participants (whites, blacks, and Hispanics), the monitoring of FBG at set time intervals, the inclusion of several measures of glycemic variability, the ascertainment of outcomes following a standardized protocol, and the accounting for mean blood glucose.

Our findings should be interpreted in the context of the following potential limitations. First, our study was observational and, thus, cannot establish causality. Second, ALLHAT was a randomized trial including participants within a limited age range, which restricts the generalizability of our findings. The extrapolation to our findings to other patient subgroups is further limited by the differences between the ALLHAT participants with serial FBG measurements included in our investigation and those excluded. Third, we did not have data on glycemic markers other than FBG, such as HbA_{1c} or 2-h postload glucose, and long-term variability in HbA_{1c} or 2-h post load glucose may provide a different and complementary perspective on the association of glycemic variability with outcomes. Indeed, in prior studies, HbA_{1c} variability has been found to be significantly associated with outcomes (4,20). Also, variability in postprandial hyperglycemia may carry a differential prognosis value than that of fasting hyperglycemia. Fourth, we did not have data on glucose-lowering medications (insulin or noninsulin therapies), especially as the use of medications, an intermittent adherence to drugs, and the modification of therapeutic regimen may influence glycemic variability. Finally, residual unmeasured confounding may have affected our estimates.

Conclusion

Our findings suggest that greater visit-to-visit glycemic variability is associated with an increased risk for all-cause mortality, over and above the effect of mean blood glucose, especially among people without diabetes. The association of visit-to-visit glycemic variability with CVD requires further investigation in novel cohorts. Future studies are needed to further elucidate the mechanisms underlying a high level of glycemic variability (which could ultimately inform a more efficacious approach to treating hyperglycemia) and to determine whether decreasing long-term glycemic variability would be associated with reduced risk of mortality.

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